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EXAMINER	
BASQUILL, SEAN M	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,435	WHITEHOUSE ET AL.	
	Examiner	Art Unit	
	Sean Basquill	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *15 Aug 2006; 20 Jun 2007; 28 Dec 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Applicant's claims for the benefit of the prior-filed applications 10/589,435 (15 August 2005), PCT/US2005/016282 (10 May 2005), and 60/569,241 (10 May 2004) under 35 U.S.C. 119(e) 120, and 365(c) are acknowledged.

Claim Rejections - 35 USC § 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or ameliorating restenosis, does not reasonably provide enablement for the prevention of restenosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to

practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level.

The invention relates to the treatment of arterial restenosis using vitamin D compounds. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites R. Hoffmann & G.S. Mintz, *Coronary In-stent Restenosis - Predictors, Treatment*

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

and Prevention, 21 EUR. HEART J. 1739 (November 2000) (indicating that although stent placement reduces restenosis compared to balloon angioplasty, restenosis still occurs in about 10-60% of cases).

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the term will be interpreted expansively. The term "prevention" may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for the prevention of arterial restenosis following angioplasty or arterial bypass surgery, other than the administration of active vitamin D compounds for restenosis treatment. The latter is corroborated by the working examples.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent restenosis as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Claim 25 refers to "the method of Claim 1, further comprising administering one or more therapeutic agents. Because Claim 1 specifies that an active Vitamin D compound should be administered, it is uncertain whether Claim 25 and Claims dependent therefrom require only the active Vitamin D compound or other, additional, therapeutic agents. Unless otherwise specified, the examiner has interpreted Claim 25 as requiring the administration of only one therapeutic agent to treat restenosis.

4. Claims 33-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33-42 contain the trademark/trade name MIGLYOL 812. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a component of a pharmaceutical composition to be used in the method as described and, accordingly, the identification/description is indefinite.

5. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Claiming both "about 50% MIGLYOL 812, about 50% vitamin E TPGS, BHA, and BHT" provides no guidance as to specifically how much of either vitamin E TPGS, BHA or BHT must be present to read upon or infringe the composition of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 6, 9, 22, 24, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Application Publication EP1270026 (hereinafter "Andersen").

Andersen discloses the intravenous placement of a drug eluting stent following balloon angioplasty to treat or ameliorate restenosis. (Para 4-6). Anderson recommends using an active vitamin D compound, such as seocalcitol (EB 1089 from Leo Pharmaceuticals), known to possess an antiproliferative effect against smooth muscle cells. (Para. 8-10, 12). While Andersen is silent as to the hypercalcemic effect of seocalcitol, the examiner asserts, and applicants admit (Specification, paragraph 32) that seocalcitol (compound EB 1089 from Leo Pharmaceuticals) inherently possesses a reduced hypercalcemic effect.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP1270026 ("Andersen") as applied to Claims 1-4, 6, 9, 22, 24, and 25, in view of U.S. Patent 6,521,608 (hereinafter "Henner").

Andersen describes the intravenous placement of a stent containing an active vitamin D compound, as discussed above, but does not specify that the active vitamin D compound is calcitriol or EB-1089, does not teach administration of an active vitamin D compound before or before and after surgery, nor are the specifically claimed doses described.

Henner discloses the treatment of hyperproliferative disorders using pulsed administration of Vitamin D compounds such as calcitriol administered using high-dose pulsed administration involving a dose of about 0.5 micrograms per kilogram of body weight at an interval of about once per week to avoid inducing hypercalcemia. (Abs.). The vitamin D compounds described by Hemmer as useful in the instant invention include calcitriol and EB-1089. (C.5, L.17-38). Hemmer indicates that the vitamin D compounds of the invention may be administered using methods and common carriers well known to those having skill in the art including compositions for injection or oral dose forms such as tablets or capsules additionally comprising common pharmaceutical adjunct materials including preservatives and the like. (C.16, L.45-67). Hemmer recommends providing unit doses containing between 5-100 micrograms of vitamin D compounds like calcitriol. (C.17, L.3-8). These doses are sufficient to establish and maintain the plasma concentration of the vitamin D compound such as calcitriol of at least about 0.5nM, such as 0.9nm or more. (C.7, L.51-58).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time of the instant invention to have substituted calcitriol or EB-1089 for the active vitamin D

compound included in the stent of Andersen. One having ordinary skill in the art would have been motivated to do so because they would have recognized the equivalence of either calcitriol or EB-1089 for the purpose of providing an active vitamin D compound in the intravenous stent of Andersen. MPEP § 2144.06.

In addition, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the instant invention to have administered intravenously or orally a vitamin D compound such as calcitriol or EB-1089 to prevent restenosis following angioplasty. One having skill in the art would have been motivated to do so because of Hemmer's teaching pulsed administration of calcitriol permits inhibition of proliferative disorders such as restenosis while avoiding the induction of hypercalcemia associated with calcitriol administration.

It would have also been *prima facie* obvious for one having ordinary skill in the art at the time of the instant invention to have, using the doses disclosed by Hemmer, optimized the vitamin D doses to obtain the instantly claimed doses of active vitamin D compounds through routine experimentation. MPEP § 2144.05(II).

Finally, in general, it is obvious to combine method steps which are individually known and complete in themselves, where the result is nothing more than that which would be expected. *In re Mostovych*, 144 USPQ 38 (CCPA 1964). Because administration of vitamin D compounds after arterial surgery is well-known, it would have been *prima facie* obvious for the skilled artisan to administer such compounds either before, after, or before and after said surgery to effect improved surgical outcomes.

8. Claims 1-26, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen as modified by Henner as applied to claims 1-25 above, and further in view of Seung-Jung Park, *et al*, *A Paclitaxel-Eluting Stent for the Prevention of Coronary Restenosis*, 348 N. ENGL. J. MED. 1537 (17 April 2003) (hereinafter "Park").

Andersen as modified by Henner discloses the use of active vitamin D compounds for the treatment of restenosis following angioplasty, but does not describe the use of additional antiangiogenic agents such as paclitaxel.

Park describes the use of paclitaxel, in particular stents coated with paclitaxel, in the treatment of restenosis and intimal hyperplasia following coronary surgery. (Pg. 1538).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time of the instant invention to have combined compounds such as paclitaxel with the calcitriol or EB-1089 included in the stent of Andersen as modified by Henner. One having ordinary skill in the art would have been motivated to do so because it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for same purpose, in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. MPEP § 2144.06.

9. Claims 1-27 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen as modified by Henner as applied to claims 1-25 above, and further in view of U.S. Patent Application Publication 2003/0125800 (hereinafter "Shulze").

Andersen as modified by Henner discloses the use of active vitamin D compounds for the treatment of restenosis following angioplasty, but does not describe the use of additional antiangiogenic agents such as tranilast.

Shulze discloses stents coated with agents to prevent restenosis following their placement. (Para. 6). Restenosis inhibitors commonly incorporated into stents include compounds such as tranilast. (Para. 9).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time of the instant invention to have combined compounds such as tranilast with the calcitriol or EB-1089 included in the stent of Andersen as modified by Henner. One having ordinary skill in the art would have been motivated to do so because it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for same purpose, in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. MPEP § 2144.06.

10. Claims 1-25 and 33-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen as modified by Henner as applied to claims 1-25 above, and further in view of U.S. Patent Application Publication 2003/0191093 (hereinafter "Chen").

Andersen as modified by Henner discloses the use of active vitamin D compounds for the treatment of restenosis following angioplasty, but does not describe a specific unit dosing form comprising various pharmaceutically acceptable excipients in specific amounts.

Chen describes pharmaceutical dosing forms including gelatin capsules (Para. 70) containing between 10-75 micrograms of a vitamin D compound (Para. 71) such as calcitriol.

(Para. 11). The unit dosing forms should contain about 50% of a lipophilic phase (Para. 74) and about 50% of surfactants. (Para. 75). Suitable lipophilic compositions include MIGLYOL 812 (Para. 42), and suitable surfactants include vitamin E TPGS. (Para. 62). In addition, the composition may include antioxidants including BHA and BHT. (Para. 67). The final unit dosing form capsule should result in a volume of between 10-1000 microliters. (Para. 72).

The specific combination of features claimed for the unit dosing form is disclosed within the broad generic ranges taught by Chen but such "picking and choosing" within several variables does not necessarily give rise to anticipation. *Corning Glass Works v. Sumitomo Elec.*, 868 F.2d 1251, 1262 (Fed. Circ. 1989). Where, as here, the reference does not provide any motivation to select this specific combination of calcitriol dose, unit dosing form size, lipophilic phase, antioxidants, and surfactants, anticipation cannot be found.

That being said, however, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR v. Teleflex*, 127 S.Ct. 1727, 1740 (2007)(quoting *Sakraida v. A.G. Pro*, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (*Id.*). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would

employ." *KSR v. Teleflex*, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." *Id.* at 1742.

Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients calcitriol dose, unit dosing form size, lipophilic phase, antioxidants, and surfactants from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement."

Having arrived at the unit dosing form of the instant claims, it would have been prima facie obvious to one having ordinary skill in the art at the time of the instant invention to have used the calcitriol dosing form of Chen in the method of preventing restenosis of Andersen as modified by Henner. One having ordinary skill in the art at the time of the instant invention would have been motivated to do so because they would have recognized the suitability of the unit dosing form of Chen for providing calcitriol dosing to treat or ameliorate restenosis following arterial stent placement or bypass surgery described by Andersen as modified by Henner.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean Basquill whose telephone number is (571) 270-5862. The examiner can normally be reached on Monday through Thursday, between 8AM and 6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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